# Activated parietal epithelial cells or dedifferentiated podocytes in FSGS: Can we make the difference?

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**To the Editor:** Dijkman *et al.*[1] did excellent work on a single specimen of transplant nephrectomy for recurrent idiopathic focal segmental glomerulosclerosis (FSGS): using immunohistochemical markers and three-dimensional (3D) reconstruction of glomeruli, they characterized the lineage of cells present in the FSGS lesions and concluded that proliferated epithelial cells originate from parietal epithelial cells (PEC). However, the possibility that these cells could, in fact, be dedifferentiated podocytes cannot be ruled out. Indeed, PEC and dedifferentiated podocytes share common phenotypes.

During nephrogenesis (reviewed by Pavenstädt *et al.*[2] and Kreidberg[3]), precursors of both podocytes and PEC express the junctional protein P-cadherin, cytokeratins and PAX2. During the maturation of glomeruli, collagen chain expression shifts from IV$\alpha$1 and $\alpha$2 to $\alpha$3, $\alpha$4 and $\alpha$5 in the glomerular basement membrane, and the podocytes acquire a mature phenotype. They loose the expression of PAX2, which is correlated with the loss of mitotic properties. They do no longer express cytokeratins and acquire specific podocyte proteins.

In the cellular variants of FSGS, the podocytes are dysregulated and dedifferentiated.[4,5] They proliferate, lose their specific proteins, and again express markers of immature podocytes as in fetal glomeruli. Thus, the expression of P-cadherin, cytokeratins, PAX2, and IV$\alpha$1 and $\alpha$2 collagens can be observed in dedifferentiated podocytes as well as in PEC. In idiopathic FSGS, PAX2 (unpublished data) and cytokeratins[4] have been detected in podocytes, covering the tuft in the absence of any synechia, particularly in the collapsing variant of FSGS or in glomeruli where the cytokeratin-negative PEC stand opposite to cytokeratin-positive dedifferentiated podocytes. This indicates that proliferated epithelial cells can be dedifferentiated podocytes and not necessarily activated PEC migrated from the Bowman's capsule. In the study of Dijkman *et al.*,[1] the damaged glomeruli shown in 3D reconstruction exhibited synechia between the tuft and capsule. Under this condition, we suggest that cells from both origins (i.e. tuft podocytes and capsular PEC) can easily be mixed and cannot be specifically identified by the immunohistochemical markers used.

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# Use of ultrahigh RAAS blockade: Implications for exacerbation of renal failure

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**To the Editor:** Rossing *et al.*,[1] lately, reported using irbesartan, up to 900 mg/day, in 52 type II diabetic microalbuminurics, compared to 300 mg/day, and showed additional renoprotection.

Recently, concern has been raised of an increasing end-stage renal disease epidemic in the USA, which was observed to coincide with the increasing use of renin-angiotensin-aldosterone system (RAAS) blockade.[2] This raises a troubling suspicion for iatrogenic end-stage renal disease.[2]

We recently reported a previously unrecognized syndrome of late-onset renal failure from angiotensin blockade in patients on stable doses of RAAS blockade.[3] Mean serum creatinine improved from $2.9 \pm 0.9$ to $1.8 \pm 0.4$ mg/dl ($P = 0.04$) following discontinuation of RAAS blockade.[3]

We are very concerned about the potential implications of the escalating and possibly uncontrolled use of ultrahigh doses of RAAS blockade. The subjects were relatively young, mean age 58 years, with normal baseline glomerular filtration rate, mean 103 ml/min/1.73 m$^2$.[1] By contrast, the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial cohort of 33 357 patients was older, mean age 67 years, with lower mean baseline glomerular filtration rate, 78 ml/min/1.73 m$^2$.[4] Furthermore, treatment with irbesartan, 900 mg/day, was only for 2 months.[1]

The general applicability of such intense and overriding total RAAS blocking strategies, particularly long term, and more so in susceptible elderly diabetic hypertensives, with lower glomerular filtration rates, is at the least very troubling. Until we understand the long-term consequences of such therapeutic maneuvers, strong caution must be advised. Finally, we recommend more long-term monitoring of kidney function in all patients on RAAS blockade, more so in the susceptible elderly population.[3]

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# Vascular calcification in chronic kidney disease: Evolving pathogenesis with progressive chronic kidney disease?

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**To the Editor:** Cozollino and colleagues present a thoughtful review on vascular calcification (VC) in chronic kidney disease (CKD) and discuss the evidence supporting a dominant role for disordered mineral metabolism in the rapid progression of calcification seen in stage 5 CKD.[1]

However, the title and the article may lead one to conclude that either VC is a major problem only in stage 5 CKD or that disordered mineral metabolism plays a dominant role across the entire spectrum of CKD. Accumulating evidence suggests that VC is present in over 90% of diabetics (and is often quite severe) and 40% of nondiabetics with CKD, long before stage 5 CKD or treatment with calcium-based phosphate binders, and this appears to be unrelated to disordered mineral metabolism.[2,3] This observation is consistent with the authors' observations that phosphorus appears to induce calcification only when its concentration in the culture media exceeds 2.0 mmol/l – levels only rarely observed in stage 3 or 4 CKD. Finally, progression of VC is observed among diabetics with CKD, over a rather short interval, long before stage 5 CKD, and this also appears to be independent of disordered mineral metabolism.[4]

Thus, the available evidence suggests that VC begins and is a significant problem early in CKD, and this is independent of disordered mineral metabolism. Relatively rapid progression of VC is demonstrable in nondialyzed diabetic CKD, the process accelerates with worsening renal function and disordered mineral metabolism likely assume a dominant role quite late in the course of CKD (probably stage 4 or 5).

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